Infections with the tick-borne bacterium "Candidatus Neoehrlichia mikurensis" mimic noninfectious conditions in patients with B cell malignancies or autoimmune diseases

Grankvist, Anna ; Andersson, Per-Ola ; Mattsson, Mattias ; Sender, Monica ; Vaht, Krista ; Höper, Linnea ; Sakiniene, Egidija ; Trysberg, Estelle ; Stenson, Martin ; Fehr, Jan ; Pekova, Sona ; Bogdan, Christian ; Bloemberg, Guido ; Wennerås, Christine

Abstract: BACKGROUND Candidatus Neoehrlichia mikurensis is a newly discovered noncultivatable bacterium spread among ticks and rodents in Europe and Asia that can infect humans, particularly immunocompromised patients. METHODS We compiled clinical and laboratory data from 11 patients with hematological malignances or autoimmune diseases who were diagnosed with Candidatus N. mikurensis infection in Europe 2010-2013. Both published (6) and unpublished cases (5) were included. RESULTS The patients had a median age of 67, were mostly male (8/11), and resided in Sweden, Switzerland, Germany, and the Czech Republic. All but one had ongoing or recent immune suppressive treatment and a majority were splenectomized (8/11). Less than half of them recalled tick exposure. The most frequent symptoms were fever (11/11), localized pain afflicting muscles and/or joints (8/11), vascular and thromboembolic events (6/11), that is, deep vein thrombosis (4), transitory ischemic attacks (2), pulmonary embolism (1), and arterial aneurysm (1). Typical laboratory findings were elevated C-reactive protein, leukocytosis with neutrophilia, and anemia. Median time from onset of symptoms to correct diagnosis was 2 months. In at least 4 cases, the condition was interpreted to be due to the underlying disease, and immunosuppressive therapy was scheduled. All patients recovered completely when doxycycline was administered. CONCLUSIONS Candidatus N. mikurensis is an emerging tick-borne pathogen that may give rise to a systemic inflammatory syndrome in persons with hematologic or autoimmune diseases that could be mistaken for recurrence of the underlying disease and/or unrelated arteriosclerotic vascular events. Awareness of this new pathogen is warranted among rheumatologists, hematologists, oncologists, and infectious disease specialists.

DOI: https://doi.org/10.1093/cid/ciu189

DOI: https://doi.org/10.1093/cid/ciu189

MAJOR ARTICLE

Infections With the Tick-Borne Bacterium "*Candidatus Neoehrlichia mikurensis*" Mimic Noninfectious Conditions in Patients With B Cell Malignancies or Autoimmune Diseases

Anna Grankvist,[1] Per-Ola Andersson,[2] Mattias Mattsson,[3] Monica Sender,[2] Krista Vaht,[2] Linnea Höper,[4] Egidija Sakiniene,[4] Estelle Trysberg,[4] Martin Stenson,[5] Jan Fehr,[6] Sona Pekova,[7] Christian Bogdan,[8] Guido Bloemberg,[9] and Christine Wennerås[1,2]

[1]Department of Clinical Microbiology/Infectious Diseases, Sahlgrenska Academy, Sahlgrenska University Hospital, Göteborg; [2]Department of Hematology and Coagulation, Sahlgrenska University Hospital, Göteborg; [3]Department of Internal Medicine, Karlstad Hospital, Karlstad; [4]Department of Rheumatology, Sahlgrenska University Hospital, Göteborg and [5]Department of Medicine, Kungälv Hospital, Kungälv, Sweden; [6]Division of Infectious Diseases and Hospital Epidemiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland; [7]Laboratory for Molecular Diagnostics, CHAMBON Laboratories, Prague, Czech Republic; [8]Mikrobiologische Institut—Klinische Mikrobiologie, Immunologie und Hygiene, Friedrich Alexander Universität Erlangen-Nürnberg and Universitätsklinikum Erlangen, Erlangen, Germany and [9]Institute of Medical Microbiology, University of Zurich, Zurich, Switzerland

Background. Candidatus *Neoehrlichia mikurensis* is a newly discovered noncultivatable bacterium spread among ticks and rodents in Europe and Asia that can infect humans, particularly immunocompromised patients.

Methods. We compiled clinical and laboratory data from 11 patients with hematological malignances or autoimmune diseases who were diagnosed with *Candidatus N.* mikurensis infection in Europe 2010–2013. Both published (6) and unpublished cases (5) were included.

Results. The patients had a median age of 67, were mostly male (8/11), and resided in Sweden, Switzerland, Germany, and the Czech Republic. All but one had ongoing or recent immune suppressive treatment and a majority were splenectomized (8/11). Less than half of them recalled tick exposure. The most frequent symptoms were fever (11/11), localized pain afflicting muscles and/or joints (8/11), vascular and thromboembolic events (6/11), that is, deep vein thrombosis (4), transitory ischemic attacks (2), pulmonary embolism (1), and arterial aneurysm (1). Typical laboratory findings were elevated C-reactive protein, leukocytosis with neutrophilia, and anemia. Median time from onset of symptoms to correct diagnosis was 2 months. In at least 4 cases, the condition was interpreted to be due to the underlying disease, and immunosuppressive therapy was scheduled. All patients recovered completely when doxycycline was administered.

Conclusions. Candidatus *N. mikurensis* is an emerging tick-borne pathogen that may give rise to a systemic inflammatory syndrome in persons with hematologic or autoimmune diseases that could be mistaken for recurrence of the underlying disease and/or unrelated arteriosclerotic vascular events. Awareness of this new pathogen is warranted among rheumatologists, hematologists, oncologists, and infectious disease specialists.

Keywords. B-cell malignancies; human; infection, *Neoehrlichia*; tick-borne.

"*Candidatus Neoehrlichia mikurensis*" was first reported to be a human pathogen in 2010 [1–3]. Until now, a total of 15 cases have been reported from Sweden, [2] Germany, [3] Switzerland, [1, 4] the Czech Republic, [5] and China [6]. A little more than half of the published cases concerned apparently healthy persons, [1, 3, 6], whereas the remainder were immunocompromised patients [2–5].

Received 24 January 2014; accepted 12 March 2014; electronically published 18 March 2014.

Correspondence: Christine Wennerås, MD, PhD, Department of Clinical Microbiology, Guldhedsgatan 10, 413 46 Göteborg Sweden (christine.wenneras@microbio.gu.se)

Clinical Infectious Diseases 2014;58(12):1716–22

DOI: 10.1093/cid/ciu189

Ca. N. mikurensis received its name in 2004, after it was discovered in ticks and rodents on the Japanese island of Mikura by means of polymerase chain reaction (PCR) directed against conserved genes of the bacterial genome, for example, 16SrRNA and *groESL* sequences [7]. Transmission electron microscopy of infected rats showed small cocci in the cytoplasm of endothelial cells [7]. Phylogenetic analyses reveal it to be a new species belonging to the family *Anaplasmataceae.* Its closest relative is *Candidatus Neoehrlichia lotoris*, which primarily infects raccoons [8]. Other related species are *Ehrlichia ruminantium*, *Ehrlichia chaffeensis,* and *Anaplasma phagocytophilum* [7, 9]. All these bacterial species are strict intracellular pathogens that can only be cultivated in cell lines. *N. mikurensis* is denominated "*Candidatus*" because no one to our knowledge has yet reported its cultivation. The target cells of *Neoehrlichia* infection in humans are yet to be defined although polymorphonuclear granulocytes [5] and endothelial cells have been implicated [9]. At present, the only diagnostic option is either pan-bacterial PCR (targeting the 16S rRNA gene) followed by sequence analysis, [2] or a specific real-time polymerase chain reaction (RT-PCR), [4] performed on whole blood, plasma, or bone marrow. No serological tests are available, and the lack of serological cross-reactivity with either *Anaplasma phagocytophilum* or *Ehrlichia chaffeensis* [3, 7] precludes the use of *Anaplasma*- or *Ehrlichia*-based indirect fluorescence antibody tests.

In retrospect, it has become clear that others have reported on the same bacterial species prior to Kawahara's original report from 2004 but under other names [10–15]. *Ca. N. mikurensis* is widely distributed among ticks (*Ixodes ricinus, I. persulcatus, I. ovatus, I. frontalis*), [8, 16] rats, field mice, and voles in Northern [12, 17, 18], Central [19–22], and Eastern Europe [16, 23, 24], Asia [7, 25, 26], and Africa [27]. No reports exist from the Americas or Australia. Rodents appear to be healthy carriers of *Ca. N. mikurensis* and may be viewed as the zoonotic reservoir [17, 28]. The only other animal species besides humans that has been shown to become sick due to *Ca. N. mikurensis* infection are dogs [29].

One peculiarity of *Neoehrlichia* infection in humans is the accumulation of cases among patients with B-cell malignancies or rheumatological diseases, many of whom have been splenectomized [2, 4, 5]. Another distinguishing feature is the high prevalence of thromboembolic complications among these patients [2–4]. Importantly, diagnosis of infection could be missed or severely delayed as the clinical picture of *Neoehrlichia* infection may be misinterpreted as noninfectious conditions, for example, arteriosclerotic thromboembolism with secondary fever, or systemic inflammation due to a new bout or recurrence of the underlying rheumatologic or hematologic disease.

The objective of this study was to provide a synopsis of new, unpublished cases of *Neoehrlichia* infection in patients with rheumatic/autoimmune diseases or hematologic malignancies (n = 5) along with already published cases (n = 6) regarding host factors, clinical picture, and laboratory findings. The goal is to make rheumatologists, hematolo/oncologists, and infectious disease specialists aware of this new infectious disease as patients may remain untreated, or even worse, be given chemotherapy and/or immune suppressive therapy against the underlying disease.

METHODS

Data Collection

All but 1 of the 6 Swedish patients reside on the west coast of Sweden, within a 100 km-radius from the city of Göteborg. They attend the rheumatology and/or hematology clinics at the Sahlgrenska University Hospital in Göteborg and Kungälv's Hospital. One patient was treated at Karlstad's Hospital. The Swedish patients have given oral or written consent to publish nonidentifiable data. Some of the patients participate in the "Neo-VÄST" study, which was approved by the Local Ethics Committee in Göteborg, Sweden.

The details on the origin, clinical recruitment, and follow-up of all other patients summarized here have been reported elsewhere [3–5].

Procedures

Clinical data have mainly been derived from the patients' journals and attending physicians in charge of the respective patients; anamnestic data were derived from the patients themselves. Some data were obtained from published patient cases [2–5]. Laboratory data were also obtained from patient charts and published case reports. GraphPad prism 5.0 software was used to calculate medians and 25/75 percentiles.

The diagnosis of *Ca. N. mikurensis* infection was in all cases based on PCR analysis of peripheral blood samples followed by sequence analysis. Specimens of bone marrow, cerebrospinal fluid, and blood culture flask contents were also tested for the presence of *Neoehrlichia* DNA. Pan-bacterial PCR directed against either the V1–V4 region (Sweden, Germany, Switzerland) [2–4] or V4–V8 region (Czech Republic) [5] of the 16S rRNA-gene was used to amplify bacterial DNA. Taqman-based real-time PCR assays targeting either parts of the *groEL* gene or the 16 SrRNA gene [2–4] of *Ca. N. mikurensis*, incorporating internal control plasmids containing the same respective gene sequences, were used to estimate the concentrations of bacterial gene copies in patients' samples.

Statistical Analyses

Statistical analyses were not performed because there was no control group for comparative analyses.

Table 1. Host Factors of 11 Patients Diagnosed With *Candidatus Neoehrlichia mikurensis* Infection

Patient	Age	Sex	Hematological Malignancy	Autoimmune disease	Immune Suppression	Asplenic	Date of Diagnosis	Country	Reference
1	77	M	B-CLL		Corticosteroids	Yes	July 2009	Sweden	[2]
2	75	M	B-CLL		Azathioprine Corticosteroids	Yes	July 2011	Sweden	This study
3	67	F	Later developed Follicular lymphoma	SLE	Corticosteroids	Yes (inborn)	July 2011	Sweden	This study
4	67	F	T-LGL	Psoriasis artropathy	Cyclophosphamide Corticosteroids	Yes	January 2013	Sweden	This study
5	54	M	None	Psoriasis	Cyclophosphamide Corticosteroids	No	January 2013	Sweden	This study
6	59	M	DLCBL	Rheumatoid arthritis	Cyclophosphamide	Yes	June 2013	Sweden	This study
7	68	M	CLL		Rituximab Corticosteroids	Yes	October 2011	Switzerland	[4]
8	58	M	Follicular lymphoma		Rituximab	No	October 2011	Switzerland	[4]
9	55	F	Mantle cell lymphoma		Rituximab Cytosinarabinoside Mitoxantrone Methothrexate	Yes	March 2008	Czech Republic	[5]
10	58	M	PTLD	Sclerosing cholangitis	Rituximab Tacrolimus	Yes	July 2009	Czech Republic	[5]
11	69	M	None	Chronic inflammatory demyelinating polyneuropathy	Rituximab Cyclophosphamide Corticosteroids	No	June 2007	Germany	[3]

Abbreviations: B-CLL, B-cell chronic lymphocytic leukemia; CLL, Chronic Lymphocytic Leukemia; DLCBL, Diffuse large cell B-cell lymphoma; F, female; M, male; PTLD, post transplant lymfoproliferative disorder; SLE, Systemic lupus erythematosus; T-LGL, T-cell large granular lymphocyte lymphoma/leukemia.

Role of Funding Source

The funding sources (Västra Götaland Regional Research and Development Fund, ALF Research Fund, and Cancer and Allergy Foundation) are noncommercial organizations that have had no impact on the design of the present study.

RESULTS

Host Factors

The 11 patients were all middle-aged or elderly (median age 67 years, range 54–77) and had an underlying disease involving the adaptive immune system (Table 1). More specifically, the patients had either malignant clonal expansion of lymphocytes, in most cases malignant lymphoma or chronic lymphocytic leukemia engaging B cells, or clonal expansion of autoreactive lymphocytes, giving rise to autoimmune diseases such as rheumatoid arthritis, systemic lupus erythematosus, or psoriasis (Table 1). Three patients first had an autoimmune disease and subsequently also developed a malignant hematological disease (patients 3, 4, and 6). A surprisingly high fraction of the patients (73%) had no spleen; in most instances it had been removed to diagnose the suspected hematologic disease (Table 1). Also, a majority of the patients had ongoing or recent (preceding 3 months) chemotherapy or immunosuppressive treatment with systemic corticosteroids and/or rituximab (anti-CD20 monoclonal antibody).

Symptoms and Clinical Signs

All patients had systemic inflammation, manifested as high fever, often spiking up to 40°C, with chills and nightly sweats (clinical signs are shown in Table 2). Another prominent finding was different types of localized pain, such as migrating muscular pain, stiff neck, tender subcutaneous veins, and joint pain engaging knees, mandibular/temporal joints, and elbows—2 of the patients with myalgia and arthralgia required opiates because the pain was not relieved by corticosteroid treatment. All but one of the patients were hospitalized, and 2 were admitted more than once until the correct diagnosis was established.

The most striking finding was the high rate of vascular and thromboembolic events associated with this infectious disease. More than half of the patients were afflicted (6/11), and some of them severely: 2 patients had deep vein thrombosis above the knee, a third patient developed deep vein thrombosis twice (upper arm and leg), and another patient developed deep vein thrombosis, pulmonary embolism, and transitory ischemic attacks. The 2 patients with transitory ischemic attacks had repeated episodes that engaged both sides of the body. One patient had severe arterial inflammation with aneurysms.

Table 2. Clinical Signs of 11 Patients Diagnosed With Neoehrlichiosis

Clinical Sign	No. of Patients	Percent
Fever	11/11	100
Chills	7/11	64
Nightly sweats	5/11	45
Pain	8/11	73
Muscular	4/11	36
Neck	3/11	27
Mandible	3/11	27
Subcutaneous veins	2/11	18
Arthralgia	2/11	18
Vascular/ thromboembolic events	6/11	54
Deep vein thrombosis	4/11	36
Transitory ischemic attack	2/11	18
Pulmonary embolism	1/11	9
Arterial aneurysm	1/11	9
Skin rash	4/11	36
Erythema nodosum	2/11	18
Erysipelas	2/11	18
Ankle edema	4/11	36
Cough	4/11	36
Weight loss	4/11	36

Possibly, the ankle swelling observed among several patients reflected local blood vessel inflammation. Two patients who did not develop any vascular or thromboembolic events were on prophylactic anticoagulation treatment at the time of diagnosis (patient 4, low-dose aspirin because of atrial fibrillation; patient 6, chronic low-molecular heparin because of repeated DVT and pulmonary embolism). Hence, multiple thromboembolic events seem to characterize *Ca. N. mikurensis* infection.

Less specific findings displayed by some patients were skin rashes of the lower extremities, that is, erythema nodosum and erysipelas, and diarrhea. Significant weight loss developed in a few patients, particularly those with systemic inflammation of long duration. Pulmonary symptoms such as cough were discrete and infrequent, and the majority of patients lacked pulmonary infiltrates on chest radiograms.

Laboratory Findings

The most abnormal laboratory findings among the routine parameters that are usually analyzed in patients with systemic inflammation are listed in Table 3. The only consistent finding among all patients was elevation of the acute phase reactant C-reactive protein in serum, with levels ranging from 4- to 74-fold higher than the cutoff level. Leukocytosis with neutrophilia and anemia were also typical findings. About half of the patients had at some point raised levels of lactate dehydrogenase in serum and hyponatremia, respectively. Lowered platelet counts and elevated transaminase concentrations were rare findings.

Diagnostics and Bacterial Load

The diagnosis of *Ca. Neoehrlichia* infection was in all cases based on pan-bacterial PCR analysis of segments of the 16S rRNA gene followed by sequence and homology analyses. EDTA- or citrate-anticoagulated peripheral blood samples were uniformly used for diagnosis, but *Neoehrlichia* DNA was also detected in plasma specimens (most patients), blood culture flask contents (patient 1) and in bone marrow samples (patients 7, 8, and 11). However, *Neoehrlichia* was not detected in cerebrospinal fluid of patient 3 despite neurologic symptoms; these symptoms were interpreted to result from infection-related transitory ischemic attacks.

Indirect estimates of the concentrations of bacteria in patient samples were performed using real-time PCR and internal control plasmids. If one assumes that *Neoehrlichia* contains only 1 copy of the 16S rRNA gene or heat shock protein gene *groEL*, bacterial concentrations were on the order of 10^6/mL blood among these patients (median value of 2×10^6 bacterial gene copies/mL in 5 assessed patients, 25/75 percentile = 0.05–7.8×10^6/mL). The levels were even higher in bone marrow: up to 35×10^7/mL (patient 7).

Diagnostic Delay

Diagnostic delay was considerable, the median number of days from the onset of symptoms to diagnosis was 60 (25/75 percentile = 26–135). All patients were subjected to extensive microbiological investigations and given empiric antibiotics. Some patients received corticosteroids because of suspected "disease fever", for example, "tumor fever" or "autoimmune fever." At least 4 of the patients had been scheduled to receive chemotherapy but narrowly escaped such treatment once *Ca. N. mikurensis* infection was diagnosed. Five of the 11 patients recalled tick bites. Three patients fell ill during winter/early spring (January–March in Europe), one of whom (patient 4) received blood transfusions prior to development of infectious symptoms (Table 1).

Response to Antibiotics

All patients had been given empiric antibiotics treatment other than doxycycline before the diagnosis of *Ca. N. mikurensis* infection was set. No response was seen to benzyl-penicillin or piperacillin/tazobactam, amoxicillin ± clavulanate, clindamycin, third-generation cephalosporines (cefotaxime, ceftazidime), aminoglycosides (gentamicin), or quinolones (ciprofloxacin and levofloxacin). A transient response to meropenem was seen in a few cases. A complete response was achieved in all patients once they were treated with doxycycline (100 mg PO BID) for 3–6 weeks. Many patients experienced dramatic and rapid improvement within 1 day of initiation of doxycycline therapy. The median time to resolution of symptoms was 5 days (25/75 percentile = 2–8).

Table 3. Laboratory Parameters of 11 Patients Diagnosed With Neoehrlichiosis

Laboratory Parameter	Level	Range of Altered Parameter	Reference Level	Unit	No. of Patients	Percent
S-C-reactive protein	↑	19–370	<5	g/L	11/11	100
White blood cell count	↑	11–26	3.5–8.8	$\times 10^9$/L	9/11	82
B-Neutrophils	↑	NR	1.8–7.5	$\times 10^9$/L	9/11	82
B-Hemoglobin	↓	85–119	117–170	g/L	9/11	82
S-Sodium	↓	127–136	137–145	mmoles/L	6/11	54
S-Lactate dehydrogenase	↑	3.9–15	1.8–3.4	μcat/L	5/11	45
B-platelet counts	↓	Slight decrease	145–348	$\times 10^9$/L	2/11	18
S-Aspartate aminotransferase	↑	Slight increase (<2-fold)	(0.25–0.75)	μcat/L	2/11	18
S-Alanine aminotransferase	↑	Slight increase (<2-fold)	(0.15–1.1)	μcat/L	2/11	18

Abbreviations: B, blood; NR, not reported; S, serum.

DISCUSSION

The purpose of this case review study was to highlight one reason for why human cases of *Neoehrlichia* infection may go unrecognized: the aberrant clinical picture seen among 2 particular groups of patients–middle-aged persons with autoimmune diseases or hematologic malignancies. First, myalgia, arthralgia, and/or fever are typical findings among patients with some of the autoimmune conditions described in this study, for example, psoriasis arthropathy, rheumatoid arthritis, or systemic lupus erythematosus. Second, if no infectious agents are discovered despite extensive microbiological investigations in patients with fever and systemic inflammation with a serious underlying condition, such as malignant lymphoma, chronic lymphatic leukemia, or autoimmune systemic rheumatic disease, the most common interpretation is that the condition reflects recurrence/deterioration of the underlying morbidity. This may ultimately result in erroneous, and potentially dangerous, administration of immune suppressive therapy such as chemotherapy, rituximab, and corticosteroids, which almost occurred in at least 4 of the cases documented in this study.

Another common finding among the *Neoehrlichia*-infected patients was the high incidence of thromboembolic/vascular complications; these were not interpreted to be the consequence of an infection but coincidental to a systemic inflammatory condition of unknown cause. In one case, fever was suspected to be secondary to widespread venous embolism [2]. As transitory ischemic attacks are quite common among older persons, it is understandable that this complication was initially seen as a separate phenomenon, not connected to the febrile episode. Finally, we report a case of arterial aneurysm in a *Neoehrlichia*-infected patient with underlying autoimmune disease. Although it is impossible to attribute causality between the development of the aneurysm and *Neoehrlichia* infection, there has been a previous report of cerebral arterial aneurysm in a purported previously healthy person with suspected *Neoehrlichia* infection, who actually died from intracerebral hemorrhage [3].

The pathogenic mechanisms behind the thromboembolic complications associated with *Neoehrlichia* infection are unknown. Is it a direct effect of infection? Does *Neoehrlichia* infect endothelial cells or exert toxic effects on the endothelium? Or is it an indirect effect of long-standing systemic inflammation with concomitant activation of coagulation [30]? Blood clot formation is a primitive infectious defense mechanism used by horse shoe crabs and other invertebrates to limit infectious processes [30]; the high rate of thromboembolic complications in our patients may have been the next best alternative for those with depressed B-cell immune responses to curb the infectious process.

The importance of the spleen in the infectious defense against *Neoehrlichia* is reflected by the high prevalence of splenectomized patients in this study. The well-known function of the spleen in the defense against encapsulated bacteria is not likely to be of relevance for *Ca. Neoehrlichia mikurensis* with its frail cell wall [7]. Instead, the spleen's importance for the generation of "natural antibodies" [31] and maintenance of immunoglobulin M (IgM) memory B cells [32] is probably more pertinent. The very high loads of bacteria in the blood of patients most likely reflect their impaired immune state. However, no patient died despite the fact that diagnostic delay was significant. Moreover, the patients recovered within a week after doxycycline therapy was initiated. It appears as if 100 mg doxycycline twice daily for a 3-week period is sufficient to clear the infection.

There are several more reasons for the paucity of reported human *Neoehrlichia* cases: (1) the bacterium does not grow in cell-free media. In fact, to date no one to our knowledge has yet succeeded in cultivating the bacterium at all, which requires the use of eukaryotic cell lines. Hence, the diagnosis relies on panbacterial or specific PCR, which are not used as first-line diagnostic procedures. (2) Awareness of this new microbe is very low among medical practitioners. (3) Some of the symptoms arising from a *Neoehrlichia* infection may be attributed to other

infectious agents such as *Borrelia*, *Anaplasma* or a random "summer virus". Doxycycline, the treatment of choice for *Neoehrlichia* infection, is equally efficient to treat infections perceived to be caused by *Borrelia*, *Anaplasma*, and *Ehrlichia* species, respectively. We propose the use of the term "neoehrlichiosis" as a complement to the longer "*Candidatus Neoehrlichia mikurensis*" infection, both in the interest of brevity, but also to focus on this new clinical infectious disease. Moreover, this nomenclature has already been used elsewhere [4].

The most likely route of transmission of the infection to humans is direct inoculation of the bacteria through the skin via the bite of infected ticks. The incubation period is unknown but has been estimated to be 5–21 days for the other human pathogenic ehrlichiae [33]. The fact that more than half of the patients were unaware of tick bite is in agreement with studies of *Borrelia*, where it is well-known that tick bites may pass unnoticed by patients [34]. Three patients apparently fell ill during winter/early spring, which was surprising as ticks are less active during this period of the year. Because one of the patients had received blood transfusions prior to the development of fever, we investigated if this might have been the route of transmission, as has been shown for *Anaplasma* [35] and *Ehrlichia* [36]. Unfortunately, no aliquot from the erythrocyte concentrate had been stored. One of the 2 blood donors claimed to have had a flulike episode prior to donation of blood; this donor tested negative for *Neoehrlichia* DNA but had recovered completely and was asymptomatic at the time of testing. Thus, we were unable to determine if blood transfusions are a possible route of *Neoehrlichia* infection.

To conclude, we hope to raise the awareness of this newly discovered microbe that may give rise to an infectious disease in elderly persons with autoimmune conditions and hematological malignancies. Physicians within the fields of rheumatology, hematology, oncology, and infectious diseases should be aware of this new infectious agent and their attention drawn to patients with suspected recurrence of the underlying autoimmune or hematologic disease where the clinical picture is atypical.

Notes

Financial support. This work was supported by Västra Götaland Regional Research and Development Fund, ALF Foundation, Strategic ALF Grant for Transplantation, the Bavarian Ministry for Environment, Health and Consumer Protection and the Swedish Cancer and Allergy Foundation.

Potential conflicts of interest. All authors: No reported conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Fehr JS, Bloemberg GV, Ritter C, et al. Septicemia caused by tick-borne bacterial pathogen *Candidatus* Neoehrlichia mikurensis. Emerg Infect Dis **2010**; 16:1127–9.
2. Welinder-Olsson C, Kjellin E, Vaht K, Jacobsson S, Wenneras C. First case of human Candidatus *Neoehrlichia mikurensis* infection in a febrile patient with chronic lymphocytic leukemia. J Clin Microbiol **2010**; 48:1956–9.
3. von Loewenich FD, Geissdorfer W, Disque C, et al. Detection of "*Candidatus Neoehrlichia mikurensis*" in two patients with severe febrile illnesses: evidence for a European sequence variant. J Clin Microbiol **2010**; 48:2630–5.
4. Maurer FP, Keller PM, Beuret C, et al. Close geographic association of human neoehrlichiosis and tick populations carrying "*Candidatus Neoehrlichia mikurensis*" in Eastern Switzerland. J Clin Microbiol **2013**; 51:169–76.
5. Pekova S, Vydra J, Kabickova H, et al. *Candidatus Neoehrlichia mikurensis* infection identified in 2 hematooncologic patients: benefit of molecular techniques for rare pathogen detection. Diagn Microbiol Infect Dis **2011**; 69:266–70.
6. Li H, Jiang JF, Liu W, et al. Human infection with *Candidatus Neoehrlichia mikurensis*, China. Emerg Infect Dis **2012**; 18:1636–9.
7. Kawahara M, Rikihisa Y, Isogai E, et al. Ultrastructure and phylogenetic analysis of '*Candidatus Neoehrlichia mikurensis*' in the family *Anaplasmataceae*, isolated from wild rats and found in *Ixodes ovatus* ticks. Int J Syst Evol Microbiol **2004**; 54(Pt 5):1837–43.
8. Yabsley MJ, Murphy SM, Luttrell MP, Wilcox BR, Ruckdeschel C. Raccoons (*Procyon lotor*), but not rodents, are natural and experimental hosts for an ehrlichial organism related to "*Candidatus Neoehrlichia mikurensis*". Vet Microbiol **2008**; 131:301–8.
9. Rar V, Golovljova I. *Anaplasma*, *Ehrlichia*, and "*Candidatus Neoehrlichia*" bacteria: Pathogenicity, biodiversity, and molecular genetic characteristics, a review. Infect Genet Evol **2011**; 11:1842–61.
10. Alekseev AN, Dubinina HV, Van De Pol I, Schouls LM. Identification of *Ehrlichia* spp. and *Borrelia burgdorferi* in *Ixodes* ticks in the Baltic regions of Russia. J Clin Microbiol **2001**; 39:2237–42.
11. Brouqui P, Sanogo YO, Caruso G, Merola F, Raoult D. *Candidatus Ehrlichia walkerii*: a new *Ehrlichia* detected in *Ixodes ricinus* tick collected from asymptomatic humans in Northern Italy. Ann N Y Acad Sci **2003**; 990:134–40.
12. Jenkins A, Kristiansen BE, Allum AG, et al. *Borrelia burgdorferi* sensu lato and *Ehrlichia* spp. in *Ixodes* ticks from southern Norway. J Clin Microbiol **2001**; 39:3666–71.
13. Pan H, Liu S, Ma Y, Tong S, Sun Y. *Ehrlichia*-like organism gene found in small mammals in the suburban district of Guangzhou of China. Ann N Y Acad Sci **2003**; 990:107–11.
14. Schouls LM, Van De Pol I, Rijpkema SG, Schot CS. Detection and identification of *Ehrlichia*, *Borrelia burgdorferi* sensu lato, and *Bartonella* species in Dutch *Ixodes ricinus* ticks. J Clin Microbiol **1999**; 37: 2215–22.
15. Shpynov S, Fournier PE, Rudakov N, Tarasevich I, Raoult D. Detection of members of the genera *Rickettsia*, *Anaplasma*, and *Ehrlichia* in ticks collected in the Asiatic part of Russia. Ann N Y Acad Sci **2006**; 1078:378–83.
16. Movila A, Alekseev AN, Dubinina HV, Toderas I. Detection of tick-borne pathogens in ticks from migratory birds in the Baltic region of Russia. Med Vet Entomol **2013**; 27:113–7.
17. Andersson M, Raberg L. Wild rodents and novel human pathogen *Candidatus Neoehrlichia mikurensis*, Southern Sweden. Emerg Infect Dis **2011**; 17:1716–8.
18. Fertner ME, Molbak L, Boye Pihl TP, Fomsgaard A, Bodker R. First detection of tick-borne "*Candidatus Neoehrlichia mikurensis*" in Denmark 2011. Euro Surveill **2012**; 17:1–3.
19. Capelli G, Ravagnan S, Montarsi F, et al. Occurrence and identification of risk areas of Ixodes ricinus-borne pathogens: a cost-effectiveness analysis in north-eastern Italy. Parasit Vectors **2012**; 5:61–70.
20. van Overbeek L, Gassner F, van der Plas CL, Kastelein P, Nunes-da Rocha U, Takken W. Diversity of *Ixodes ricinus* tick-associated bacterial communities from different forests. FEMS Microbiol Ecol **2008**; 66:72–84.

21. Vayssier-Taussat M, Le Rhun D, Buffet JP, et al. *Candidatus Neoehrlichia mikurensis* in bank voles, France. Emerg Infect Dis **2012**; 18:2063–5.
22. Lommano E, Bertaiola L, Dupasquier C, Gern L. Infections and coinfections of questing *Ixodes ricinus* ticks by emerging zoonotic pathogens in Western Switzerland. Appl Environ Microbiol **2012**; 78:4606–12.
23. Movila A, Toderas I, Uspenskaia I, Conovalov J. Molecular detection of tick-borne pathogens in *Ixodes ricinus* from Moldova collected in 1960. Ticks Tick Borne Dis **2013**; 4:359–61.
24. Spitalska E, Boldis V, Kostanova Z, Kocianova E, Stefanidesova K. Incidence of various tick-borne microorganisms in rodents and ticks of central Slovakia. Acta Virol **2008**; 52:175–9.
25. Li H, Jiang J, Tang F, et al. Wide distribution and genetic diversity of "*Candidatus Neoehrlichia mikurensis*" in rodents from China. Appl Environ Microbiol **2013**; 79:1024–7.
26. Rar VA, Epikhina TI, Livanova NN, et al. Study of the heterogeneity of 16s rRNA gene and *groESL* operone in the dna samples of *Anaplasma phagocytophilum*, *Ehrlichia muris*, and "*Candidatus* Neoehrlichia mikurensis" determined in the *Ixodes persulcatus* ticks in the area of Urals, Siberia, and far east of Russia. Mol Gen Mikrobiol Virusol **2011**; 26:17–23.
27. Kamani J, Baneth G, Mumcuoglu KY, et al. Molecular detection and characterization of tick-borne pathogens in dogs and ticks from Nigeria. PLoS Negl Trop Dis **2013**; 7:e2108.
28. Silaghi C, Woll D, Mahling M, Pfister K, Pfeffer M. *Candidatus Neoehrlichia mikurensis* in rodents in an area with sympatric existence of the hard ticks *Ixodes ricinus* and *Dermacentor reticulatus*, Germany. Parasit Vectors **2012**; 5:285–92.
29. Diniz PP, Schulz BS, Hartmann K, Breitschwerdt EB. "*Candidatus Neoehrlichia mikurensis*" infection in a dog from Germany. J Clin Microbiol **2011**; 49:2059–62.
30. Delvaeye M, Conway EM. Coagulation and innate immune responses: can we view them separately? Blood **2009**; 114:2367–74.
31. Ochsenbein AF, Fehr T, Lutz C, et al. Control of early viral and bacterial distribution and disease by natural antibodies. Science **1999**; 286:2156–9.
32. Kruetzmann S, Rosado MM, Weber H, et al. Human immunoglobulin M memory B cells controlling *Streptococcus pneumoniae* infections are generated in the spleen. J Exp Med **2003**; 197:939–45.
33. Thomas RJ, Dumler JS, Carlyon JA. Current management of human granulocytic anaplasmosis, human monocytic ehrlichiosis and *Ehrlichia ewingii* ehrlichiosis. Expert Rev Anti Infect Ther **2009**; 7:709–22.
34. Hengge UR, Tannapfel A, Tyring SK, Erbel R, Arendt G, Ruzicka T. Lyme borreliosis. Lancet Infect Dis **2003**; 3:489–500.
35. Alhumaidan H, Westley B, Esteva C, Berardi V, Young C, Sweeney J. Transfusion-transmitted anaplasmosis from leukoreduced red blood cells. Transfusion **2013**; 53:181–6.
36. Regan J, Matthias J, Green-Murphy A, et al. A confirmed *Ehrlichia ewingii* infection likely acquired through platelet transfusion. Clin Infect Dis **2013**; 56:e105–7.